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Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

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PATENT- OG VAREMÆRKESTYRELSEN

Compounds comprising LPA

Field of invention

The present invention relates to compounds capable of binding to fibroblast growth factor receptor (FGFR), said compounds comprising a ligand presenting assembly (LPA) comprising a FGFR ligand and obtainable by a method for preparing said LPA enabling presentation of amino acid sequence(s) of said FGFR ligands for the receptor binding. The invention discloses amino acid sequences of FGFR ligands, which presentation using the LPA method is advantageous for stimulation or inhibition of FGFR activation of said receptor by these ligands. Invention also relates to pharmaceutical compositions comprising an LPA comprising one or more sequences of the invention and use of said composition for the treatment or prevention of different pathological conditions wherein the FGFR activation or inhibition is involved.

Description of invention

The present invention relates to a ligand presenting assembly (LPA) comprising a ligand comprising at least one peptide fragment having an amino acid sequence of the formula

L1-A-L2-B-L3-C-L4-D-L5, wherein

one of A, B, C, D is selected from a hydrophobic amino acid residue,

one of A, B, C, D is selected from a basic amino acid residue or Ser, Thr, Asn or Gln,

one of A, B, C, D is selected from an acidic amino acid residue or Ser, Thr, Asn or Gln,

one of A, B, C, D is Gly or Ala, and

L1, L2, L3, L4 and L5 is selected from a chemical bond or an amino acid sequence having n amino acid residues, wherein n is an integer of from 0 to 5,

wherein the ligand is a ligand for a functional cell surface receptor.

In a preferred embodiment the invention relates to a functional cell surface receptor being fibroblast growth factor receptor (FGFR), wherein a LPA presents different FGFR ligands. In a preferred embodiment a FGFR ligand is FGL peptide (SEQ ID NO: 1).

The LPA comprising a ligand of the FGFR is according to the present invention obtained by a method for preparing an LPA enabling presentation of peptide sequence(s) of FGFR ligands of the invention (SEQ ID NOS: 1-146) comprising the steps of

(a) providing by solid phase synthesis or fragment coupling ligands comprising desired sequence(s), the ligands being attached to a solid phase,

(b) if nessesary, deprotecting any N-terminal amino acid groups while th eligands/s) are still attached to the solid phase,

(c) reacting the ligand(s) having unprotected N-terminal groups with an achiral di- tri- or tetracarboxylic acid so as to provide a construct having a ring structure, and

(d) cleaving the construct from the solid phase so as to provide an LPA comprising ligands having free C-terminal groups.

The invention further concerns a pharmaceutical composition comprising an LPA comprising an FGFR ligand selected from the sequences set forth in SEQ ID NO: 1-146.

Another aspect of the invention concerns the use an LPA comprising an FGFR ligand for the manufacture of a medicament

- for the treatment of conditions of the central and peripheral nervous system associated with postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression; for treatment of diseases or conditions of the muscles including conditions with impaired function of neuro-muscular connections, such as after organ transplantation, or such as genetic or traumatic atrophic muscle disorders; or for treatment of diseases or conditions of various organs, such as degenerative conditions of the gonads, of the pancreas such as diabetes mellitus type I and II, of the kidney such as nephrosis and of the heart, liver and bowel;

- for the treatment of postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression;

- for the promotion of wound-healing;
- for the treatment of cancer;
- for the prevention of death of heart muscle cells, such as after acute myocardial infarction, or after angiogenesis;
- for revascularsation;
- for the stimulation of the ability to learn and/or the short and/or long-term memory.
- for the prevention of cell death due to ischemia;
- for the prevention of body damages due to alcohol consumption;
- for the treatment of prion diseases.

Description of Drawings

Figure 1 presents an HPLC elution profile of the FGL peptide (SEQ ID NO: 1) as a lysin-bound dendromer

Figure 2 shows a flow chart of LPA sysntesis

Figure 3 shows structural formula of FGL peptide (SEQ ID NO:1) synthesised as a tetrameric dendrimer (FGL_D) (A). FGL dimer that has two FGL_M coupled to a lysine through their C-terminal ends ($FGL_{dimer\text{-}lysine}$) (B) and LPA comprising FGL dimer (FGL_L) that has the N-terminal end of FGL coupled to an amine diacetyl and has the C-terminal end amidated (C).

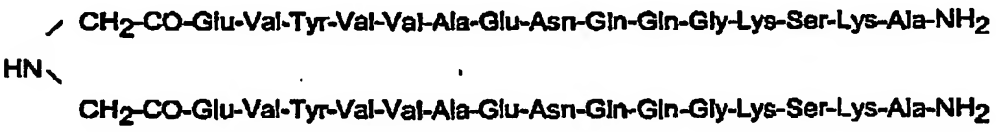
Examples

Example 1. Synthesis of an LPA presenting two copies of FGL (SEQ ID NO: 1), HN(CH2CO-EVYVVAENQQGKSKA-NH2)2.

The sequence EVYVVAENQQGKSKA was assembled on TentaGel S RAM resin (90 mg, 0.22 mmol/g). The resin was placed in a polyethylene vessel equipped with a polypropylene filter for filtration. The rewsin was swelled in DMF (xx ml), and treated with 20% piperidine in DMF to secure the presence of non-protected amino groups on the resin. The resin was drained and washed with DMF until no yellow color could bedetected after addition of Dhbt-OH to the drained DMF.

Example 2. Description of the synthesis of FGLL

FGLL has the structural formula:



It consists of two identical 15 amino acid peptides, forming a dimer through a linker molecule.

Solid Phase Synthesis

The peptide chain is synthesized by the standard Fmoc-solid phase method. The solid phase synthesis is performed on Tentagel resin with a Rink amide linker, to which the first (C-terminal) amino acid is attached. The amino acids are coupled one at a time alternating with removal of Fmoc-groups. The amino acid derivatives used are, (in the following order):

Fmoc-Ala-OH
Fmoc-Lys(Boc)-OH
Fmoc-Ser(tBu)-OH
Fmoc-Lys(Boc)-OH
Fmoc-Gly-OH
Fmoc-Gln(Trt)-OH

Fmoc-Gln(Trt)-OH
Fmoc-Asn(Trt)-OH
Fmoc-Glu(tBu)-OH
Fmoc-Ala-OH
Fmoc-Val-OH
Fmoc-Val-OH
Fmoc-Tyr(tBu)-OH
Fmoc-Val-OH
Fmoc-Glu(tBu)-OH

The Fmoc-amino acids are preactivated in DMF by TBTU /HOBt and then coupled to the growing peptide-resin. For the removal of Fmoc-groups piperidine in DMF is used. At the end of the solid phase synthesis, the peptide resin looks as follows:

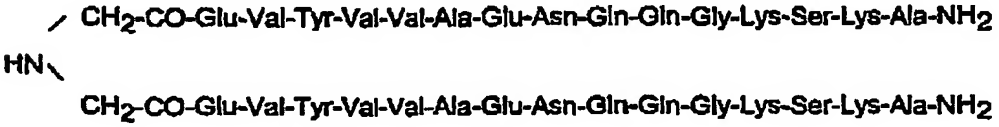
Glu(tBu)-Val-Tyr(tBu)-Val-Val-Ala-Glu(tBu)-Asn(Trt)-Gln(Trt)-Gln(Trt)-Gly-Lys(Boc)-Lys(Boc)-Ser(tBu)-Lys(Boc)-Ala-R

Dimerisation

The dimer is created by coupling Boc-iminodiacetic acid to the peptide on the resin, using TBTU/HOBt. To reduce sidereactions multiple coupling are performed with Boc-iminodiacetic acid as the limiting component.

Cleavage

The peptide is simultaneously cleaved from the resin and deprotected on the side chains in TFA with addition of TES and water as scavengers to yield the peptide amide:



The amount of TFA is reduced by evaporation and the peptide precipitated.

The peptide is purified by reversed phase HPLC. The product is finally isolated by lyophilisation.

Starting materials, reagents and solvents used in the production of FGLL

Acetic acid
Acetic acid anhydride
O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
Boc-iminodiacetic acid
t-Butyl methyl ether
Dimethylformamide
Ethanol, 99,9%
N-Ethyl-diisopropylamine
Fmoc-Ala-OH
Fmoc-Asn(Trt)-OH
Fmoc-Gln(Trt)-OH
Fmoc-Glu(tBu)-OH
Fmoc-Gly-OH
Fmoc-Lys(Boc)-OH
Fmoc-Ser(tBu)-OH
Fmoc-Tyr(tBu)-OH
Fmoc-Val-OH
1-Hydroxybenzotriazol
Isopropanol
N-methylpyrrolidone
1-Octanol
Piperidine
Trifluoroacetic acid
Triethylsilane

Abbreviations

Abbreviations for amino acids are in accordance with the recommendations in the IUPAC-IUB Joint Commission on Biochemical Nomenclature Eur. J. Biochem, 1984, vol. 184, pp 9-37

Other abbreviations:

AcOH	Acetic acid
TBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
Ida	Boc iminodiacetic acid
MTBE	t-Butyl methyl ether
DMF	Dimethylformamide
EtOH	Ethanol, 99,9%
DIPEA	N-Ethyl-diisopropylamine
HOBt	1-Hydroxybenzotriazol
NMP	N-methylpyrrolidone
TFA	Trifluoroacetic acid
TES	Triethylsilane
Boc	N-tertButyl oxycarbonyl
Fmoc	9-Fluorenylmethyloxycarbonyl
tBu	tert-Butyl
HPLC	High pressure liquid chromatography
R	Amide-TG-resin
AA	Amino acid

Claims

1. A ligand presenting assembly (LPA) comprising a ligand comprising at least one peptide fragment having an amino acid sequence of the formula L1-A-L2-B-L3-C-L4-D-L5, wherein
one of A, B, C, D is selected from a hydrophobic amino acid residue,
one of A, B, C, D is selected from a basic amino acid residue or Ser, Thr, Asn or Gln,
one of A, B, C, D is selected from an acidic amino acid residue or Ser, Thr, Asn or Gln,
one of A, B, C, D is Gly or Ala, and
L1, L2, L3, L4 and L5 is selected from a chemical bond or an amino acid sequence having n amino acid residues, wherein n is an integer of from 0 to 5.

2. The LPA according to claim 1, wherein the ligand is a ligand for a functional cell surface receptor.

3. The LPA according to claim 2, wherein the functional cell surface receptor is a receptor selected from the family of fibroblast growth factor receptors (FGFRs) comprising FGFR1, FGFR2, FGFR3 and FGFR4, or functional homologues thereof.

4. The LPA according to claim 1, wherein the amino acid sequence is derived from the sequence of a polypeptide selected from the group comprising cell adhesion molecules, cell-surface receptors, heparan sulphate proteoglycans, and metallo-proteases, extracellular matrix molecules or growth factors.

5. The LPA according to the claim 4, wherein the cell adhesion molecule is selected from the group comprising
- Neural Cell Adhesion Molecule (NCAM) (Swiss-Prot Ass. Nos: P13591, P13595-01, P13595),
- Neural cell adhesion molecule L1 (Swiss-Prot Ass. Nos: Q9QYQ7, Q9QY38, P11627, Q05695, P32004),
- Neural Cell Adhesion Molecule-2 (NCAM-2) (Swiss-Prot Ass. No: P36335)
- Neuron-glia Cell Adhesion Molecule (Ng-CAM) (Swiss-Prot Ass. No: Q03696;

Q90933).

- Neural cell adhesion molecule CALL (Swiss-Prot Ass. No: O00533),
- Neuroglian (Swiss-Prot Ass. No: P91767, P20241),
- Nr-CAM (HBRAVO, NRCAM, NR-CAM 12) (Swiss-Prot Ass. Nos: Q92823, O15179, Q9QVN3
- Axonin-1/TAG-1 (Swiss-Prot Ass. Nos: Q02246, P22063, P28665),
- Axonal-associated Cell Adhesion Molecule (AxCAM) (NCBI Ass. No: NP_031544.1; Swiss-Prot Ass. No: Q8TC35),
- Myelin-Associated Glycoprotein (MAG) (Swiss-Prot Ass. No: P20917),
- Neural cell adhesion molecule BIG-1 (Swiss-Prot Ass. No: Q62682),
- Neural cell adhesion molecule BIG-2 (Swiss-Prot Ass. No: Q62845),
- Fasciclin (FAS-2) (Swiss-Prot Ass. No: P22648),
- Neural cell adhesion molecule HNB-3/NB-3 (Swiss-Prot Ass. Nos: Q9UQ52, P97528, Q9JMB8)
- Neural cell adhesion molecule HNB-2/NB-2 (Swiss-Prot Ass. Nos: O94779, P07409, P97527),
- Cadherin (Swiss-Prot Ass. No: Q9VW71),
- Junctional Adhesion Molecule-1 (JAM-1) (Swiss-Prot Ass. Nos: Q9JKD5, O88792),
- Neural cell adhesion F3/F11(Contactin) (Swiss-Prot Ass. Nos: Q63198, P1260, Q12860, Q28106, P14781, O93250),
- Neurofascin (Swiss-Prot Ass. Nos: Q90924, Q91Z60; O42414),
- B-lymphocyte cell adhesion molecule CD22 (Swiss-Prot Ass. Nos: Q9R094, P20273),
- Neogenin (NEO1) (Swiss-Prot Ass. Nos: Q92859, P97603, Q90610, P97798),
- Intercellular Cell Adhesion Molecule-5 (ICAM-5/telencephalin) (Swiss-Prot Ass. Nos: Q8TAM9, Q60625) or
- Galactose binding lectin-12 (galectin-12) (Swiss-Prot Ass. Nos: Q91VD1, Q9JKX2, Q9NZ03),
- Galactose binding lectin-4 (galectin-4) (Swiss-Prot Ass. No: Q8K419; P38552),

or fragments, or variants thereof.

6. The LPA according to the claim 4, wherein the functional cell-surface receptor is selected from the group comprising

- Fibroblast Growth Factor Receptor 1 (FGFR1) (Swiss-Prot Ass. Nos: Q9QZM7,

Q99AVV7, Q9UD50, Q63827),

- Fibroblast Growth Factor Receptor 2 (FGFR2) (Swiss-Prot Ass. Nos: Q96KM2, P21802, Q63241),
- Fibroblast Growth Factor Receptor 3 (FGFR3) (Swiss-Prot Ass. Nos: Q95M13, AF487554, Q99052),
- Fibroblast Growth Factor Receptor 4 (FGFR4) (Swiss-Prot Ass. No: Q91742),
- Neurotrophin Tyrosin Kinase Type-2 (NTRKT-2) (Swiss-Prot Ass. No: Q8WXJ5),
- Leukocyte Antigen Related Protein-Tyrosine Phosphatase (LAR-PTPRF) (Swiss-Prot Ass. Nos: Q9EQ17, Q64605, Q64604, Q9QW67, Q9VIS8 P10586),
- Nephrin (Swiss-Prot Ass. Nos: Q925S5, Q9JIX2, Q9ET59, Q9R044, Q9QZS7, Q06500),
- Protein-Tyrosine Phosphatase Receptor type S (PTPRS) (Swiss-Prot Ass. Nos: Q64699, Q13332, O75870),
- Protein-Tyrosine Phosphatase Receptor type kappa (R-PTP-kappa) (Swiss-Prot Ass. No: Q15262),
- Protein-Tyrosine Phosphatase Receptor type D (PTPRD) (Swiss-Prot Ass. Nos: Q8WX65, Q9IAJ1, P23468, Q64487),
- Ephrin type-A receptor 8 (EPHA8/Tyrosine-Protein Kinase Receptor EEK) (Swiss-Prot Ass. Nos: O09127, P29322),
- Ephrin type-A receptor 3 (EPHA8/Tyrosine-Protein Kinase Receptor ETK-1/CEK4) (Swiss-Prot Ass. No: P29318),
- Ephrin type-A receptor 2 (Swiss-Prot Ass. No: Q8N3Z2)
- Insulin Receptor (IR) (Swiss-Prot Ass. No: Q9PWN6)
- Insulin-like Growth Factor-1 Receptor (IGF-1) (Swiss-Prot Ass. Nos: Q9QVW4, P08069, P24062, Q60751, P15127, P15208)
- Insulin-related Receptor (IRR) (Swiss-Prot Ass. No: P14616),
-Tyrosine-Protein Kinase Receptor Tie-1 (Swiss-Prot Ass. Nos: 06805, P35590, Q06806),
- Roundabout receptor-1 (robo-1) (Swiss-Prot Ass. Nos: O44924, AF041082, Q9Y6N7),
- Neuronal nicotinic acetylcholine receptor alpha 3 subunit (CHRNA3) (Swiss-Prot Ass. Nos: Q8VHH6, P04757, Q8R4G9, P32297)
- Neuronal acetylcholine receptor alpha 6 subunit (Swiss-Prot Ass. Nos:

Q15825, Q9R0W9)
- Platelet-Derived Growth Factor Receptor Beta (PDGFRB) (Swiss-Prot Ass. Nos: Q8R406, Q05030),
- Interleukin-6 Receptor (IL-6R) (Swiss-Prot Ass. No: Q00560),
- Interleukin-23 Receptor (IL-23R) (Swiss-Prot Ass. No: AF461422),
- Beta-common cytokine receptor of IL-3, IL5 and GmCsf (Swiss-Prot Ass. No: P32927)
- Cytokine Receptor-Like molecule 3 (CRLF1) (Swiss-Prot Ass. No: Q9JM58),
- Class I Cytokine Receptor (ZCYTOR5) (Swiss-Prot Ass. No: Q9UHH5)
- Netrin-1 receptor DCC (Swiss-Prot Ass. No: P43146),
- Leukocyte Fc Receptor-like Protein (IFGP2) (Swiss-Prot Ass. Nos: Q96PJ6, Q96KM2),
- Macrophage Scavenger Receptor 2 (MSR2) (Swiss-Prot Ass. No: Q91YK7), or
- Granulocyte Colony Stimulating Factor Receptor (G-CSF-R) (Swiss-Prot Ass. No: Q99062),

or fragments, or variants thereof.

7. The LPA according to the claim 4, wherein the heparan sulphate proteoglycan is perlecan (Swiss-Prot Ass. No: P98160), or a fragment, or a variant thereof.

8. The compound according to the claim 4, wherein the metalloprotease is selected from the group comprising
- ADAM-8 (Swiss-Prot Ass. No: Q05910),
- ADAM-19 (Swiss-Prot Ass. Nos: Q9H013, O35674),
- ADAM-8 (Swiss-Prot Ass. No: P78325),
- ADAM-12 (Swiss-Prot Ass. Nos: O43184, Q61824),
- ADAM-28 (Swiss-Prot Ass. Nos: Q9JLN6, Q61824, Q9XSL6, Q9UKQ2),
- ADAM-33 precursor (Swiss-Prot Ass. Nos: Q8R533, Q923W9),
- ADAM-9 (Swiss-Prot Ass. Nos: Q13433, Q61072),
- ADAM-7 (Swiss-Prot Ass. NoS: Q9H2U9, O35227, Q63180),
- ADAM-1A Fertilin alpha (Swiss-Prot Ass. No: Q8R533),
- ADAM-15 (Swiss-Prot Ass. Nos: Q9QYV0, O88839, Q13444),
- Metalloproteinase-desintegrin domain containing protein (TECAM) (Swiss-Prot Ass. No: AF163291),
- Metalloproteinase 1 (Swiss-Prot Ass. Nos: O95204, Q9BSI6),

or fragments, or variants thereof.

9. The LPA according to the claim 4, wherein the extracellular matrix molecule is selected from the group comprising
   - Collagen type VII (Swiss-Prot Ass. No: Q63870),
   - Fibronectin (Swiss-Prot Ass. Nos: Q95KV4, Q95KV5, P07589, Q28377, U42594, O95609, P11276), or
   - Tenascin-R (Swiss-Prot Ass. Nos: Q15568, O00531, Q90995, P10039).

   or fragments, or variants thereof.

10. The LPA according to the claim 4, wherein the growth factor is Cytokine-like factor-1 (CLF-1) (Swiss-Prot Ass. No:O75462), or a fragment, or a variant thereof.

11. The LPA according to claims 1 to 10, wherein the peptide fragment is having an amino acid sequence selected from
    EVYVVAENQQGKSKA (SEQ ID NO 1),
    NIEVWVEAENALGKKV (SEQ ID NO: 2),
    ATNRQGKVKAFAHL (SEQ ID NO: 3),
    RYVELYVVADSQEFQK (SEQ ID NO: 4)
    VAENSRGKNVAKG (SEQ ID NO: 5),
    GEYWCVAENQYGQR (SEQ ID NO: 6),
    RLAALNGKGLGEIS (SEQ ID NO: 7),
    KYIAENMKAQNVAKEI (SEQ ID NO: 8),
    TIMGLKPETRYAVR (SEQ ID NO: 9),
    KGLGEISAATEFKT (SEQ ID NO: 10),
    NMGIWVQAENALG (SEQ ID NO: 11),
    IWVQAENMLG (SEQ ID NO: 12),
    EIWVEATNRLG (SEQ ID NO: 13),
    VWVQAANALG (SEQ ID NO: 14),
    EVWIEKDPAKGRI (SEQ ID NO: 15),
    ATNKGGEVKKNGHL (SEQ ID NO: 16),
    KYVELYLVADYLEFQK (SEQ ID NO: 17),
    RYVELYVVVDNAEFQ (SEQ ID NO: 18),
    KYVELVIVADNREFQR (SEQ ID NO: 19).

KYIEYYLVLDNGEFKR (SEQ ID NO: 20),
RYLELYIVADHTLF (SEQ ID NO: 21),
KYVEMFVVVNHQRFQ (SEQ ID NO: 22) .
RYVELFIVVDKERY (SEQ ID NO: 23),
KYVELFIVADDTVYRR (SEQ ID NO: 24),
KFIELFVVADEYVYRR (SEQ ID NO: 25),
KIVEKVIVADNSEVRK (SEQ ID NO: 26),
VELVIVADHSEAQK (SEQ ID NO: 27),
VAENSRGKNIAKG (SEQ ID NO: 28),
IAENSRGKNVARG (SEQ ID NO: 29),
AENSRGKNSFRG (SEQ ID NO: 30),
IASNLRGRNLAKG (SEQ ID NO: 31),
IPENSLGKTYAKG (SEQ ID NO: 32),
IAENMKAQNEAK (SEQ ID NO: 33),
QFIAENMKSHNETKEV (SEQ ID NO: 34),
GEYWCVAKNRVGQ (SEQ ID NO: 35),
GSYTCVAENMVGK (SEQ ID NO: 36);
GKYVCVGTNMVGER (SEQ ID NO: 37),
GNYTCVVENEYG (SEQ ID NO: 38),
GEYTCLAGNSIG (SEQ ID NO: 39),
QYYCVAENGYG (SEQ ID NO: 40),
GEYYQEAEQNGYG (SEQ ID NO: 41),
GNYTCLVENEYG (SEQ ID NO: 42),
GMYQCLAENAYG (SEQ ID NO: 43),
GMYQCAENTHG (SEQ ID NO: 44),
GIYYCLASNNYG (SEQ ID NO: 45),
GGYYCTADNSYG (SEQ ID NO: 46),
GEYQCFARNDYG (SEQ ID NO: 47),
GEYFCLASNKMG (SEQ ID NO: 48),
GEYQCFARNKFG (SEQ ID NO: 49),
GEYFCLASNKMG (SEQ ID NO: 50),
GGYYCTADNNYG (SEQ ID NO: 51),
GNYSCEAENAWGTK (SEQ ID NO: 52),
GEYTCLAENSLG (SEQ ID NO: 53),
GEYECVAENGRLG (SEQ ID NO: 54),

GNYTCVVENKFGR (SEQ ID NO: 55),
GEYTCLAGNSIG (SEQ ID NO: 56),
GEYFCVASNPIG (SEQ ID NO: 57),
EYTCIANNQAGE (SEQ ID NO: 58),
GMYQCVAENKHLG (SEQ ID NO: 59),
GEYMCTASNTIGQ (SEQ ID NO: 60),
EYVCIAENKAGEQ (SEQ ID NO: 61),
GDYTLIAKNEYGK (SEQ ID NO: 62),
GFYQCVAENEAG (SEQ ID NO: 63),
GKYECVATNSAGTR (SEQ ID NO: 64),
GEYFCVYNNSLG (SEQ ID NO: 65),
GEYECAATNAHGR (SEQ ID NO: 66),
GAYWCQGTNSVGK (SEQ ID NO: 67),
GTYSCVAENILG (SEQ ID NO: 68),
RVAAVNGKGQGDYS (SEQ ID NO: 69),
RVAAINGCGIGPFS (SEQ ID NO: 70),
AVLNGKGLG (SEQ ID NO: 71),
ALNGQGLGATS (SEQ ID NO: 72),
RLAAKNRAGLGE (SEQ ID NO: 73),
RLGVVTGKDLGEI (SEQ ID NO: 74),
TVTGLKPETSYMVK (SEQ ID NO: 75),
TLTGLKPSTRYRI (SEQ ID NO: 76),
TLTGLQPSTRYRV (SEQ ID NO: 77),
TLLGLKPDTTYDIK (SEQ ID NO: 78),
TLQGLRPETAYELR (SEQ ID NO: 79),
TLRGLRPETAYELR (SEQ ID NO: 80),
TLMNLRPKTGYSVR (SEQ ID NO: 81),
TVSGLKPGTRY (SEQ ID NO: 82),
TISGLKPDTTY (SEQ ID NO: 83),
TLQGLKPDTAY (SEQ ID NO: 84),
LRGLKPWTQYAV (SEQ ID NO: 85),
IDGLEPDTEYIVR (SEQ ID NO: 86),
LQGLKPWTQYAI (SEQ ID NO: 87),
TITGLEPGTEYTIQ (SEQ ID NO: 88),
GLKPWTQYAV (SEQ ID NO: 89).

TLASLKPWTQYAV (SEQ ID NO: 90),
LMGLQPATEYIV (SEQ ID NO: 91),
KGMGPMSEAVQFRT (SEQ ID NO: 92),
TLTGLKPDTTYDVK (SEQ ID NO: 93),
ISGLQPETSYSL (SEQ ID NO: 94),
TLLGLKPDTTYDIK (SEQ ID NO: 95),
TISGLTPETTYSI (SEQ ID NO: 96),
GNYSCLAENRLGR (SEQ ID NO: 97),
GNYTCVVENRVG (SEQ ID NO: 98),
GTYHCVATNAHG (SEQ ID NO: 99),
LSHNGVLTGYLLSY (SEQ ID NO: 100),
NGVLTGYVLRY (SEQ ID NO: 101),
NGVLTGYNLRY (SEQ ID NO: 102),
NGNLTGYLLQY (SEQ ID NO: 103),
VDENGVLTGYKIYY (SEQ ID NO: 104),
THNGALVGYSVRY (SEQ ID NO: 105),
NGILTEYILKY (SEQ ID NO: 106),
NGILIGYTLRY (SEQ ID NO: 107),
THSGQITGYKIRY (SEQ ID NO: 108),
NGKITGYIIYY (SEQ ID NO: 109),
LSHNGIFTLY (SEQ ID NO: 110),
NGILTEYTLKY (SEQ ID NO: 111),
LDPNGIITQYEISY (SEQ ID NO: 112),
NGKITGYIIYY (SEQ ID NO: 113),
HLEVQAFNGRGSGPA (SEQ ID NO: 114),
HLTVRAYNGAGYGP (SEQ ID NO: 115),
HLSVKAYNSAGTGPS (SEQ ID NO: 116),
HLAVKAYNSAGTGPS (SEQ ID NO: 117),
NLEVRAFNSAGDGP (SEQ ID NO: 118),
HLTVLAYNSKGAGP (SEQ ID NO: 119),
LRVLVFNGRGDGP (SEQ ID NO: 120),
HIDVSAFNSAGYGP (SEQ ID NO: 121),
HLAVELFNGR (SEQ ID NO: 122),
LELQSINFLGGQPA (SEQ ID NO: 123),
HFTVRAYNGAGYGP (SEQ ID NO: 124),

HLEVQAFNGRGSQPA (SEQ ID NO: 125),
VIADQPTFVKYLIK (SEQ ID NO: 126),
TIKGLRPGVVYEGQ (SEQ ID NO: 127),
TLTELSPSTQYTVK (SEQ ID NO: 128),
TLDDLAPDTTYLVQ (SEQ ID NO: 129),
TVSDVTPHAIYTVR (SEQ ID NO: 130),
IIRGLNASTRYLFR (SEQ ID NO:131),
TLMNLRPKTGYSVR (SEQ ID NO:132),
TLTGLKPGTEYEVR (SEQ ID NO: 133),
GPEHLMPSSTYVAR (SEQ ID NO: 134),
RVTGLTPKKTYEFR (SEQ ID NO: 135),
LTGLKPGTEYEFR (SEQ ID NO: 136),
EVRVQAVNGGGNGPP (SEQ ID NO: 137),
LIKVVAINDRGE (SEQ ID NO: 138),
VVSIIAVNGREE (SEQ ID NO: 139),
VVSVYAQNQNGE (SEQ ID NO: 140),
TISLVAEKGRHK (SEQ ID NO: 141),
HLEVQAFNGRGSGPA (SEQ ID NO: 142),
HVEVQAFNGRGLGPA (SEQ ID NO: 143),
HVEVQAFNGRGLGPA (SEQ ID NO: 144),
EFRVRAVNGAGEG (SEQ ID NO: 145), or
VARVRTRLAPGSRLS (SEQ ID NO: 146), or
fragments, or variants, or homologues thereof.

12. The LPA according to claim 11, wherein the sequence is EVYVVAENQQGKSKA (SEQ ID NO: 1).

13. The LPA according to claim 11, wherein the sequence is NIEVWVEAE-NALGKKV (SEQ ID NO: 2).

14. The LPA according to any of the preceding claims, wherein the LPA presents a ligand comprising at least two independent peptide fragments having the sequences selected from the sequences as defined in claim 11.

15. The LPA according to claim 14, wherein the sequences are represented by two identical copies of any of the sequences as defined in claim 11.

16. The LPA according to claim 14, wherein the sequences are represented by two different sequences selected from the sequences as defined in claim 11.

17. The LPA according to claim 15, wherein the sequences are represented by two identical copies of the sequence EVYVVAENQQGKSKA (SEQ ID NO: 1).

18. The LPA according to claim 15, wherein the sequences are represented by two identical copies of the sequence NIEVWVEAENALGKKV (SEQ ID NO: 2).

19. The LPA according to claim 16, wherein the sequences being EVYV-VAENQQGKSKA (SEQ ID NO: 1) and NIEVWVEAENALGKKV (SEQ ID NO: 2).

20. The LPA according to any of the preceding claims, wherein said LPA is obtained by a method for preparing an LPA enabling presentation of sequence(s) as defined in claim 11 comprising the steps of
    (e) providing by solid phase synthesis or fragment coupling ligands comprising desired sequence(s), the ligands being attached to a solid phase,
    (f) if nessesary, deprotecting any N-terminal amino acid groups while th eligands/s) are still attached to the solid phase,
    (g) reacting the ligand(s) having unprotected N-terminal groups with an achiral di- tri- or tetracarboxylic acid so as to provide a construct having a ring structure, and
    (h) cleaving the construct from the solid phase so as to provide an LPA comprising ligands having free C-terminal groups.

21. A pharmaceutical composition comprising an LPA as defined in claims 1-20.

22. Use an LPA as defined in claims 1-20 for the manufacture of a medicament for treatment of conditions of the central and peripheral nervous system associated with postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as

multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression; for treatment of diseases or conditions of the muscles including conditions with impaired function of neuro-muscular connections, such as after organ transplantation, or such as genetic or traumatic atrophic muscle disorders; or for treatment of diseases or conditions of various organs, such as degenerative conditions of the gonads, of the pancreas such as diabetes mellitus type I and II, of the kidney such as nephrosis and of the heart, liver and bowel.

23. Use an LPA as defined in claims 1-20 for the manufacture of a medicament for the treatment of postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression.

24. Use an LPA as defined in claims 1-20 for the manufacture of a medicament for the promotion of wound-healing.

25. Use an LPA as defined in claims 1-20 for the manufacture of a medicament for the treatment of cancer

26. wherein the cancer is any type of solid tumors requiring neoangiogenesis

27. Use an LPA as defined in claims 1-20 for the manufacture of a medicament for the prevention of death of heart muscle cells, such as after acute myocardial infarction, or after angiogenesis

28. Use an LPA as defined in claims 1-20 for the manufacture of a medicament for revascularsation.

29. Use an LPA as defined in claims 1-20 for the manufacture of a medicament for the stimulation of the ability to learn and/or the short and/or long-term memory

30. Use an LPA as defined in claims 1-20 for the manufacture of a medicament for the prevention of cell death due to ischemia.

31. Use an LPA as defined in claims 1-20 for the manufacture of a medicament for the prevention of body damages due to alcohol consumption.

32. Use an LPA as defined in claims 1-20 for the manufacture of a medicament for the treatment of prion diseases.

Chromatogram AD2003-110, RD280-01,

1g, 6g and 85g

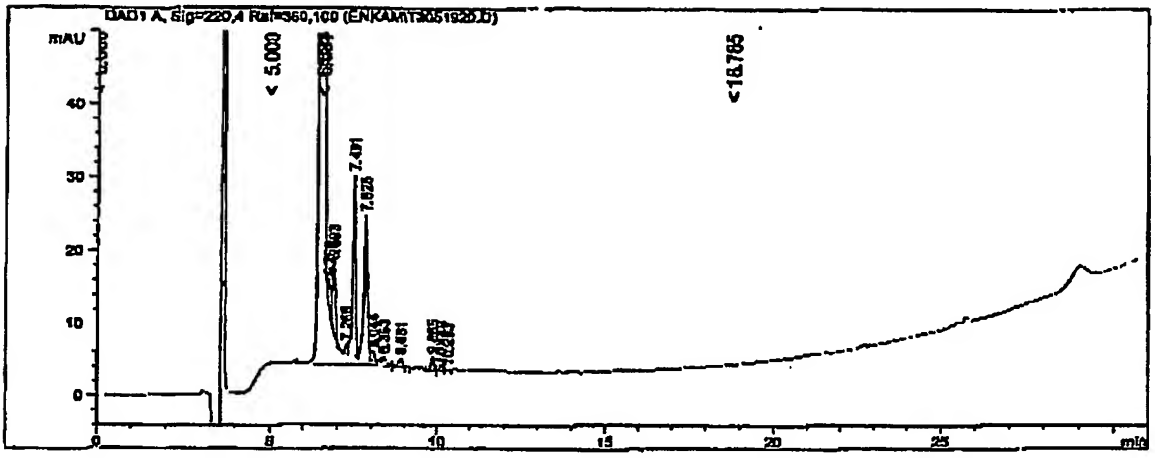


Figure 1

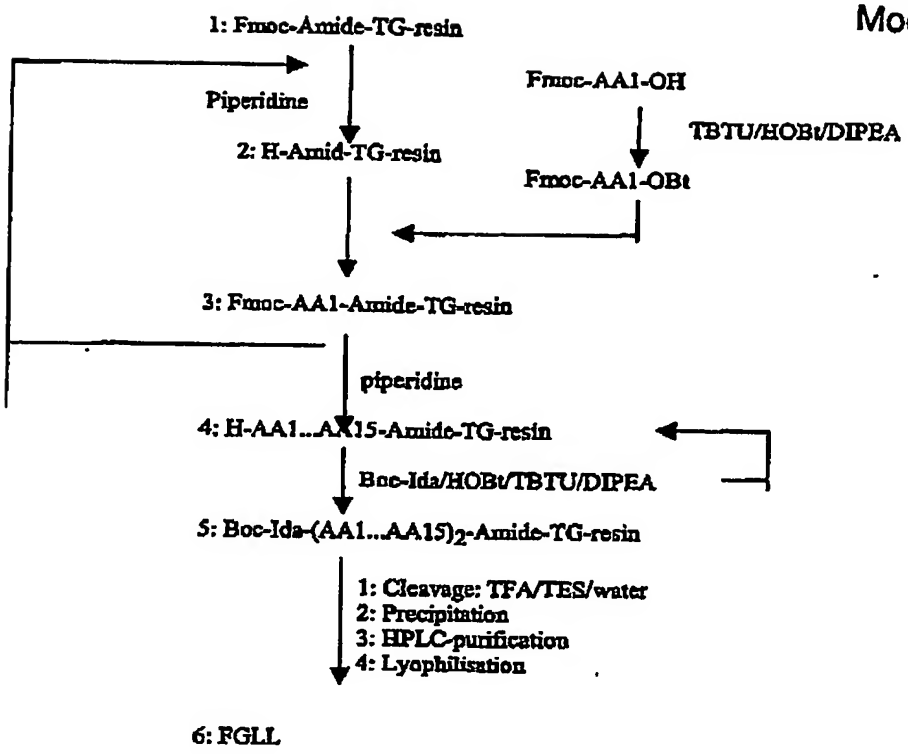


Figure 2

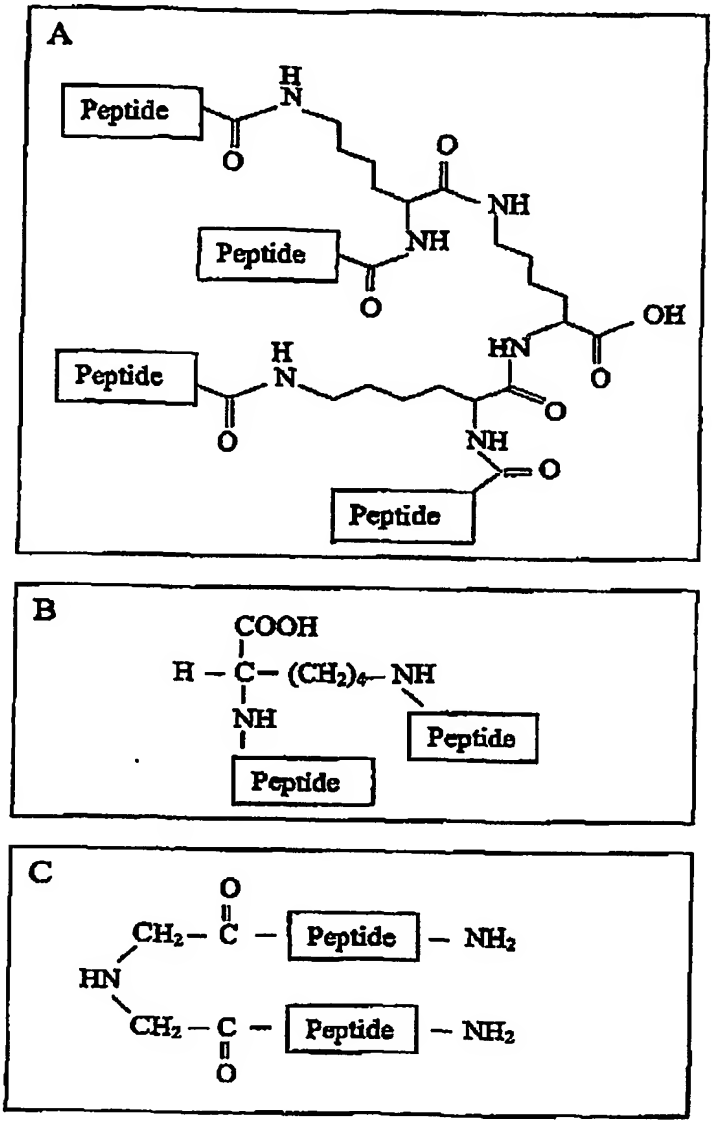


Figure 3